

ENT COOPERATION TRI

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 20 July 2001 (20.07.01)	Applicant's or agent's file reference X-13047
International application No. PCT/US00/30944	Priority date (day/month/year) 11 November 1999 (11.11.99)
International filing date (day/month/year) 09 November 2000 (09.11.00)	
Applicant FLEISCH, Jerome, Herbert et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 07 May 2001 (07.05.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Zakaria EL KHODARY Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 13 October 1998 (13.10.98)	
International application No. PCT/US98/05453	Applicant's or agent's file reference 15280-3171PC
International filing date (day/month/year) 19 March 1998 (19.03.98)	Priority date (day/month/year) 20 March 1997 (20.03.97)
Applicant FITZGERALD, David et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

25 September 1998 (25.09.98)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Pamella AMALLO-ELOTU
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/70, C07K 19/00, C12N 1/21, C07K 16/28, C12N 15/62, A61K 47/48, G01N 33/577, 33/68, A61K 51/10	A1	(11) International Publication Number: WO 98/41641 (43) International Publication Date: 24 September 1998 (24.09.98)
(21) International Application Number: PCT/US98/05453 (22) International Filing Date: 19 March 1998 (19.03.98) (30) Priority Data: 60/041,437 20 March 1997 (20.03.97) US (71) Applicant (for all designated States except US): THE GOVERNMENT OF THE UNITED STATES as represented by THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; Bethesda, MD 20892 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): FITZGERALD, David [US/US]; 1202 Azalea Drive, Rockville, MD 20852 (US). PASTAN, Ira [US/US]; 11710 Beall Mountain Road, Potomac, MD 20892-4255 (US). MANSFIELD, Elizabeth [US/US]; Apartment 408, 4710 Bethesda Avenue, Bethesda, MD 20814 (US). KREITMAN, Robert [US/US]; 11915 Reynolds Avenue, Potomac, MD 20854 (US). (74) Agents: WEBER, Ellen, L. et al.; Townsend and Townsend and Crew LLP, 8th floor, Two Embarcadero Center, San Francisco, CA 94111-3834 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: RECOMBINANT ANTIBODIES AND IMMUNOCONJUGATES TARGETED TO CD-22 BEARING CELLS AND TUMORS		
(57) Abstract Methods and compositions relating to recombinant anti-CD22 antibodies with high binding affinity, and immunoconjugates comprising the anti-CD22 antibody linked to a therapeutic agent such as a <i>Pseudomonas</i> exotoxin or a detectable label. The invention provides diagnostic methods, and means to inhibit the growth of malignant B cells.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

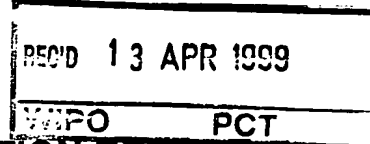
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
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BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
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BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
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BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference 15280-3171PC	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/05453	International filing date (day/month/year) 19/03/1998	Priority date (day/month/year) 20/03/1997
International Patent Classification (IPC) or national classification and IPC C12N15/70		
Applicant THE GOVERNMENT OF THE UNITED STATES... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 25/09/1998	Date of completion of this report 08.04.99
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Hinchliffe, P Telephone No. (+49-89) 2399 8431 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/05453

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-52 as originally filed

Claims, No.:

1-39 as originally filed

Drawings, sheets:

1/10-10/10 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 22-32,37-39.

because:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US98/05453

- ☒ the said international application, or the said claims Nos. 22-32,37-39 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 8,10,16
	No:	Claims 1-7,9,11-15,17-21,33-36
Inventive step (IS)	Yes:	Claims
	No:	Claims 8,10,16
Industrial applicability (IA)	Yes:	Claims 1-36
	No:	Claims

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US98/05453

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US98/05453

SECTION III

1. As noted in the I.S.R., the subject matter of claims 22-32, 37-39 concerns methods of treatment of a human or animal. According to Rule 67.1(iv) PCT such methods need not be examined by the IPEA.

SECTION V

- i. The priority document was not available at the time that this report was written. Consequently the document cited as 'PX' in the I.S.R. could become relevant to the question of novelty with respect to the subject matter of claims 1-7,9,11-15,17-21,33-36 in subsequent proceedings.
1. The subject matter of claims 1-7,9,11-15,17-21,33-36 does not fulfil the requirements of Article 33(3) PCT because it is not novel.
D1 (Proc. of the American Association for Cancer Research (1997), vol.38, p.28, abs.187, R.Kreitman et al) discloses the RFB4 based immunoconjugate. The immunoconjugate is the same as that presently disclosed (see description p.18).
2. The subject matter of claims 8,10, 16 does not appear to fulfill the requirements of Article 33(3) PCT.
D2 (Biochemistry (1994), vol.33, p.5451-5459, Y.Reiter et al) discloses on p. 5451, col.1 the instability of V_H and V_L regions derived from antibodies. The solution to this problem is to use a peptide linker to form a single chain Fv (scFv). It would appear that the need for a bond between the V_H and V_L regions is necessary for stability and either a disulfide bond or a peptide linker may be used in order to stabilise the construct. Therefore the skilled person would, without the need to exercise inventive skill, be aware from D2 that the disulfide bonded molecule disclosed in D1 could also be stabilised using a peptide linker.

SECTION VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 is not mentioned in the description, nor is this document identified therein.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US98/05453

SECTION VIII

1. Although the term "substantially similar" is clarified in the description (p.12), the claims 18-21 incorporating this term are still believed to be unclear contrary to the requirements of Article 6 PCT. The degree of homology, as calculated by the method given in the description, equivalent to substantially similar means nothing to a skilled person without knowledge of this said calculation. Consequently the claims should be clarified by replacement with the method given on p.12 of the description.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/05453

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/70 C07K19/00 C12N1/21 C07K16/28 C12N15/62
A61K47/48 G01N33/577 G01N33/68 A61K51/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	R. KREITMAN ET AL.: "The activity of disulfide-stabilized recombinant immunotoxin RFB4(dsFv)-PE38 towards human CD22+ lymphoma/leukemia xenografts in mice and fresh cells from patients." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 38, March 1997, page 28 XP002075139 USA see abstract #187	1-7, 9, 11-15, 17-29, 31, 33-36
Y	---	8, 10, 16, 30, 32, 37-39
	-/-	

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

20 August 1998

Date of mailing of the international search report

01/09/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Nooij, F

INTERNATIONAL SEARCH REPORT

1 nal Application No
PCT/US 98/05453

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>J. DE KRUIF ET AL.: "Biosynthetically lipid-modified human scFv fragments from phage display libraries as targeting molecules for immunoliposomes." FEBS LETTERS, vol. 399, no. 3, 16 December 1996, pages 232-236, XP002075140 Amsterdam, NL see the whole document ---</p>	8, 10, 16, 30, 32, 37-39
Y	<p>Y. REITER ET AL.: "Stabilization of the Fv fragments in recombinant immunotoxins by disulfide bonds engineered into conserved framework regions." BIOCHEMISTRY, vol. 33, no. 18, 10 May 1994, pages 5451-5459, XP002075141 Washington, DC, USA see abstract see figure 1 see page 5453, left-hand column, line 22 - right-hand column, line 9 ---</p>	1-39
Y	<p>R. KREITMAN ET AL.: "Pseudomonas exotoxin-based immunotoxins containing the antibody LL2 or LL2-Fab' induce regression of subcutaneous human B-cell lymphoma in mice." CANCER RESEARCH, vol. 53, no. 4, 15 February 1993, pages 819-825, XP002075142 Baltimore, MD, USA see abstract see page 819, left-hand column, line 10 - right-hand column, line 10 see page 823, right-hand column, line 30 - page 824, left-hand column, line 11 ---</p>	1-39
A	<p>C-T. KUAN ET AL.: "Recombinant immunotoxin containing a disulfide-stabilized Fv directed at erbB2 that does not require proteolytic activation." BIOCHEMISTRY, vol. 35, no. 9, 5 March 1996, pages 2872-2877, XP002075143 Washington, DC, USA see abstract ----- -/--</p>	1-39

INTERNATIONAL SEARCH REPORT

1 nal Application No
PCT/US 98/05453

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>V. RAJAGOPAL ET AL.: "A form of anti-Tac(Fv) which is both single-chain and disulfide-stabilized for imaging CD25+ tumors."</p> <p>PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 8, March 1997, page 27 XP002075144 USA see abstract #180</p> <p style="text-align: center;">---</p>	1-39
A	<p>D. LUO ET AL.: "Vl-linker-Vh orientation-dependent expression of single chain Fv containing an engineered disulfide-stabilized bond in the framework regions."</p> <p>JOURNAL OF BIOCHEMISTRY, vol. 118, no. 4, 1 October 1995, pages 825-831, XP002075145 Tokyo, Japan see abstract see figure 2</p> <p style="text-align: center;">---</p>	1-39
A	<p>M. RODRIGUES ET AL.: "Development of a humanized disulfide-stabilized anti-p185HER2 Fv-beta-lactamase fusion protein for activation of a cephalosporin doxorubicin prodrug."</p> <p>CANCER RESEARCH, vol. 55, no. 1, 1 January 1995, pages 63-70, XP002075146 Baltimore, MD, USA see abstract see figure 2</p> <p style="text-align: center;">---</p>	1-39
A	<p>E. MANSFIELD ET AL.: "Characterization of RFB4-Pseudomonas exotoxin A immunotoxins targeted to CD22 on B-cell malignancies."</p> <p>BIOCONJUGATE CHEMISTRY, vol. 7, no. 5, September 1996, pages 557-563, XP002075147 Washington, DC, USA see abstract</p> <p style="text-align: center;">---</p>	1-39
P,X	<p>E. MANSFIELD ET AL.: "Recombinant RFB4 immunotoxins exhibit potent cytotoxic activity for CD22-bearing cells and tumors."</p> <p>BLOOD, vol. 90, no. 5, 1 September 1997, pages 2020-2026, XP002075148 New York, NY, USA see the whole document</p> <p style="text-align: center;">-----</p>	1-7,9, 11-15, 17-29, 31,33-36

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 05453

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see sheet "Further information continued from PCT/ISA/210"
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ US 98/05453

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 22,23, 25-32 (all partially, as far as an in vivo method is concerned) and claim 24 (completely) are directed to a method of treatment of the human/animal body, and although claims 37 and 38 (both partially, as far as an in vivo method is concerned) and claim 39 (completely) are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 15280-3171PC	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 98/ 05453	International filing date (day/month/year) 19/03/1998	(Earliest) Priority Date (day/month/year) 20/03/1997
Applicant THE GOVERNMENT OF THE UNITED STATES aset al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (see Box I).
2. ☐ Unity of invention is lacking (see Box II).
3. ☒ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
 - ☐ filed with the international application.
 - ☒ furnished by the applicant separately from the international application,
 - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - ☐ Transcribed by this Authority
4. With regard to the title,
 - ☒ the text is approved as submitted by the applicant
 - ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - ☒ the text is approved as submitted by the applicant
 - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
 - Figure No. _____ ☐ as suggested by the applicant.
 - ☐ because the applicant failed to suggest a figure.
 - ☐ because this figure better characterizes the invention.
 - ☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 05453

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see sheet "Further information continued from PCT/ISA/210"
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/05453

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/70 C07K19/00 C12N1/21 C07K16/28 C12N15/62
A61K47/48 G01N33/577 G01N33/68 A61K51/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	R. KREITMAN ET AL.: "The activity of disulfide-stabilized recombinant immunotoxin RFB4(dsFv)-PE38 towards human CD22+ lymphoma/leukemia xenografts in mice and fresh cells from patients." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 38, March 1997, page 28 XP002075139 USA see abstract #187	1-7, 9, 11-15, 17-29, 31, 33-36
Y	---	8, 10, 16, 30, 32, 37-39
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☒ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

20 August 1998

Date of mailing of the international search report

01/09/1998

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
✓	J. DE KRUIF ET AL.: "Biosynthetically lipid-modified human scFv fragments from phage display libraries as targeting molecules for immunoliposomes." FEBS LETTERS, vol. 399, no. 3, 16 December 1996, pages 232-236, XP002075140 Amsterdam, NL see the whole document ---	8,10,16, 30,32, 37-39
Y	Y. REITER ET AL.: "Stabilization of the Fv fragments in recombinant immunotoxins by disulfide bonds engineered into conserved framework regions." BIOCHEMISTRY, vol. 33, no. 18, 10 May 1994, pages 5451-5459, XP002075141 Washington, DC, USA see abstract see figure 1 see page 5453, left-hand column, line 22 - right-hand column, line 9 ---	1-39
Y	R. KREITMAN ET AL.: "Pseudomonas exotoxin-based immunotoxins containing the antibody LL2 or LL2-Fab' induce regression of subcutaneous human B-cell lymphoma in mice." CANCER RESEARCH, vol. 53, no. 4, 15 February 1993, pages 819-825, XP002075142 Baltimore, MD, USA see abstract see page 819, left-hand column, line 10 - right-hand column, line 10 see page 823, right-hand column, line 30 - page 824, left-hand column, line 11 ---	1-39
A	C-T. KUAN ET AL.: "Recombinant immunotoxin containing a disulfide-stabilized Fv directed at erbB2 that does not require proteolytic activation." BIOCHEMISTRY, vol. 35, no. 9, 5 March 1996, pages 2872-2877, XP002075143 Washington, DC, USA see abstract --- -/--	1-39

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	V. RAJAGOPAL ET AL.: "A form of anti-Tac(Fv) which is both single-chain and disulfide-stabilized for imaging CD25+ tumors." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 8, March 1997, page 27 XP002075144 USA see abstract #180	1-39
A ✓	D. LUO ET AL.: "V1-linker-Vh orientation-dependent expression of single chain Fv containing an engineered disulfide-stabilized bond in the framework regions." JOURNAL OF BIOCHEMISTRY, vol. 118, no. 4, 1 October 1995, pages 825-831, XP002075145 Tokyo, Japan see abstract see figure 2	1-39
A ✓	M. RODRIGUES ET AL.: "Development of a humanized disulfide-stabilized anti-p185HER2 Fv-beta-lactamase fusion protein for activation of a cephalosporin doxorubicin prodrug." CANCER RESEARCH, vol. 55, no. 1, 1 January 1995, pages 63-70, XP002075146 Baltimore, MD, USA see abstract see figure 2	1-39
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